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REVIEW

RNA-binding proteins and long noncoding RNAs in intestinal epithelial autophagy and barrier function

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ABSTRACT

The intestinal autophagy and barrier function are crucial for maintaining the epithelium homeostasis and tightly regulated through well-controlled mechanisms. RNA-binding proteins (RBPs) and long noncoding RNAs (lncRNAs) modulate gene expression at the posttranscription level and are intimately involved in different physiological processes and diverse human diseases. In this review, we first highlight the roles of several RBPs and lncRNAs in the regulation of intestinal epithelial autophagy and barrier function, particularly focusing on the emerging evidence of RBPs and lncRNAs in the control of mRNA stability and translation. We additionally discuss recent findings that the interactions between RBPs and lncRNAs alter the fate of their target transcripts and thus influence gut epithelium host defense in response to stressful environments. These exciting advances in understanding the posttranscriptional control of the epithelial autophagy and barrier function by RBPs and lncRNAs provide a strong rationale for developing new effective therapeutics based on targeting RBPs and/or lncRNAs to preserve the intestinal epithelial integrity in patients with critical illnesses.

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Introduction

The mammalian intestine is colonized with a diverse population of bacteria and exposed to a wide array of luminal noxious substances and pathogens. Although most bacteria perform many beneficial functions, they can threaten host health upon tissue invasion. The intestinal epithelium directly interfaces with these diverse bacteria and noxious substances and acts as the first line of defenses against bacterial penetration and limiting the contact of luminal toxic substances with the subepithelial tissue.[1–4] Intestinal epithelial cells (IECs) are connected by apical intercellular junctional complexes, named as tight junctions (TJs) and adherens junctions (AJs), and establish a selectively permeable barrier that prevents even small molecules from leaking between cells.[2,3,5] The specialized IECs such as Goblet and Paneth cells secrete mucus and antimicrobial proteins that protect the epithelium from intrusion by luminal noxious substances, allergens, and microbial pathogens.[4,6] However, certain luminal pathogens can evade this first line of innate defense and enter epithelial cells. Epithelial cell-intrinsic innate immune responses are therefore necessary to limit the invasion of pathogens and play an important role in maintaining epithelial homeostasis.[4,7] Autophagy is an evolutionally conserved process by which cytoplasmic pathogens and unwanted materials are targeted to the lysosome for degradation.[7–9] Autophagy activity is regulated via tightly controlled mechanisms, and more than 30 autophagy-related genes (ATGs) have been identified in mammals.[8,9] Autophagy is crucial for the recognition and degradation of intracellular pathogens and functions as an innate barrier of infection, whereas its deregulation impairs intestinal epithelial defense and integrity.[3,10–12]

Posttranscriptional processes, particularly altered mRNA stability and translation by RNA-binding proteins (RBPs) and noncoding RNAs (ncRNAs), are major mechanisms by which IECs control gene expression in response to stressful environments.[13–16] After transcription from their genes, mRNAs are subjected to multiple processing and regulatory steps that are tightly controlled by numerous nuclear and cytoplasmic factors. RBPs are a large family of over 2000 proteins that bind to

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transcripts in all manner of RNA-driven processes and regulate stability and translation of target mRNAs positively or negatively.[15–18] The structures and mechanisms that RBPs use to interact with and modulate RNAs are incredibly diverse. RBP associations with different RNAs range from single protein-RNA element interaction to the assembly of multiple RBPs and RNA molecules. Long ncRNAs (lncRNAs) are defined as transcripts spanning >200 nucleotides in length and intimately involved in every level of gene regulation, including chromatin remodeling, transcriptional and post-transcriptional processes, and protein metabolism.[19,20] An increasing body of evidence indicates that RBPs and lncRNAs are a novel class of master posttranscriptional regulators of intestinal epithelium homeostasis and that disrupted regulation of RBPs and lncRNAs compromises the intestinal epithelium integrity and contributes to the pathogenesis of various gut mucosal disorders such as inflammatory bowel diseases (IBD), infection, cancers, and sepsis.[19,21–23] In this review, we highlight the important roles of several RBPs and lncRNAs in the regulation of intestinal epithelial autophagy and barrier function and further discuss in some detail the mechanisms through which RBPs and lncRNAs and their interactions modulate the stability and translation of target mRNAs.

RBPs in posttranscriptional regulation of autophagy

Control of mRNA stability and translation involves the interaction of specific mRNA sequences (cis element) with specific trans-acting factors including RBPs.[17,18] AU-rich elements (AREs) and GU-rich elements (GREs) located at the 3′-untranslated regions (3′-UTRs) of target mRNAs are the best-characterized *cis*-acting sequences and identified in ~10% of the mRNAs in human and other mammals. RBPs directly interact with AREs and/or GREs or other unknown binding sequences via their special binding domains such as RNA recognition motif (RRM) and dsRNA binding domain and regulate gene expression at the posttranscription level.[24,25] Some RBPs have housekeeping functions and interact with different cellular transcripts, but many RBPs interact with specific subsets of mRNAs and regulate gene expression levels in response to pathophysiological stresses. RBPs, including CUG-binding protein 1 (CUGBP1), AU-binding factor 1 (AUF1), tristetraprolin (TTP), BRF1, and KH-domain RNA binding protein (KSRP), enhance the decay of mRNAs and repress translation of target transcripts.[16,21] Conversely, the Hu/embryonic lethal and abnormal vision (ELAV) family of RBPs, which consists of three primary neuronal members (HuB, HuC, and HuD) and one ubiquitous member HuR, stabilize mRNAs and stimulate their translation.[26] Significant changes in the binding affinity of RBPs for target mRNAs, defects and mutations in their binding regions, and deregulation of RBP expressions and subcellular distribution occur commonly in different human diseases.[16,27,28] Using intestinal epithelial tissue-specific knockout mouse models and approaches delivering and/or transfecting RBP transgenes or specific small interfering RNAs (siRNAs), several RBPs are shown to play an essential role in regulating the intestinal epithelial autophagy and barrier function via distinct mechanisms.

HuR regulates autophagy by altering ATG expression

HuR is one of best-studied RBPs and has two N-terminal RRMs through which it binds with high affinity and specificity to AREs located in the 3′-UTRs of labile mRNAs.[29–31] In the intestinal epithelium, HuR is distributed predominantly in the nucleus of unstimulated cells but can be rapidly translocated to the cytoplasm where it interacts directly with target mRNAs in response to various stresses, thus altering the gene expression levels. Several studies have shown that HuR regulates autophagy by altering ATG expression.[32–34] HuR silencing inhibits autophagosome formation and decreases autophagic flux. Autophagosome is a double-membrane vesicle that contains sequestered cytoplasmic cargo and transports them to the lysosome.[35,36] Autophagosome formation depends on products of the *Atg* genes and is essential for autophagy activation. Mechanistically, HuR directly binds to mRNAs encoding ATG5, ATG12, and ATG16, mostly via their 3′-UTRs, enhances their stability and translation, and increases cellular abundances of ATG proteins. In support of these findings, HuR expression levels

positively correlate with the levels of ATG5 and ATG12 in various cancer cells.[33]

ATG16L1, a product of the *Atg16l1* gene, plays an important role in the intestinal epithelium homeostasis partially by interacting with A20 and orchestrating interleukin-22 signaling.[37,38] ATG16L1 also inhibits necroptosis in the intestinal epithelium[39] and protects against TNF-induced apoptosis during chronic colitis in mice.[40] Genome-wide association studies demonstrate the presence of several polymorphisms and mutations in the *Atg16l1* gene in patients with IBD and other gut mucosal injury-associated disorders.[7,12] We examined changes in the levels of HuR and ATGs in human intestinal mucosa and show that mucosal tissue samples from patients with IBD have reduced abundances of both HuR and ATG16L1. HuR is localized at both the cytoplasm and nucleus in the human intestinal epithelium of control individuals, but these HuR immunoreactive signals in the mucosal tissues from IBD patients decrease remarkably, particularly in the cytoplasm, when compared with those observed in control individuals. Importantly, the decreased levels of HuR in the intestinal mucosa are accompanied by a specific reduction in the levels of ATG16L1 in patients with IBD. In controls, both ATG16L1 and ATG5 are found predominantly in the cytoplasm of the intestinal mucosa, but ATG16L1 levels in the mucosal tissues from IBD patients decrease especially without significant changes in ATG5 content. Notably, the decreased levels of HuR and ATG16L1 are associated with mucosal injury/erosions, inflammation, delayed repair, and gut barrier dysfunction.[34,37,38,41]

To define the exact function of HuR in the regulation of ATG16L1 expression *in vivo*, we generated intestinal epithelium tissue-specific HuR knockout (IE-HuR$^{-/-}$) mice.[42] HuR is undetectable in the intestinal mucosa of IE-HuR$^{-/-}$ mice, although it is found at wild-type levels in other tissues and organs such as gastric mucosa, lung, heart, liver, and pancreas. Targeted deletion of HuR in mice does not alter the overall morphology or structure of the small and large intestines. Conditional HuR deletion in mice markedly decreases the levels of ATG16L1 in the small intestinal mucosa, but it fails to alter tissue ATG5 abundance.[34] ATG16L2 level in the intestinal mucosa of both IE-HuR$^{-/-}$ and littermate mice are too low to be detected. The basal level of ATG7 in the intestinal mucosa is relatively low but it is also reduced in HuR-ablated mice. Consistently, the levels of autophagy proteins, microtubule-associated protein light chain 3 (LC3)-I and LC3-II, also decrease in the intestinal mucosa of IE-HuR$^{-/-}$ mice relative to control littermates. Targeted deletion of HuR does not alter transcription of the *Atg* genes, because the levels of all *Atg16l1, Atg5*, and *Atg7* mRNAs in the intestinal mucosa of IE-HuR$^{-/-}$ mice are indistinguishable from those observed in control littermate mice. In addition, IE-HuR$^{-/-}$ mice also exhibit inhibited IEC proliferation and mucosal atrophy of the small intestine and delayed repair of damaged mucosa induced by mesenteric ischemia/reperfusion (I/R) in the small intestine and by dextran sulfate sodium (DSS) in the colon.[42,43] Together, these results from experiments conducted in mice and human tissues strongly suggest that HuR plays an important role in the regulation of autophagy in the intestinal epithelium and that deregulation of HuR-mediated ATG16L1 expression disrupts the epithelium-host defense, thus contributing to the pathological process of IBD in human.

HuR is required for Paneth cell function

Paneth cells reside at the bottom of the crypts in the small intestine and are crucial for maintaining homeostasis of the epithelium by engendering host protection from enteric pathogens.[6,7] Paneth cells produce abundant antibacterial proteins or peptides, including lysozyme, Reg3 lectins, α-defensin, and phospholipase A2. It has been reported that Paneth cells secrete lysozyme through secretory autophagy to limit bacterial infection of the intestine.[44] A recent study reveals that HuR is required for normal Paneth cell function and that HuR-regulated Paneth cells is critical for intestinal epithelial defense.[41] Intestinal tissues from IE-*HuR*$^{-/-}$ mice have reduced numbers of Paneth cells, and Paneth cells exhibit fewer lysozyme granules per cell, compared with tissues from control mice, but there are no effects on differentiation of Goblet cells or enterocytes. This defect in Paneth cell function is associated with repressed autophagic clearance, as shown by the decreased response of LC3 activation

to rapamycin in the HuR-deficient epithelium. Importantly, intestinal mucosa from patients with IBD also exhibits reduced levels of HuR and fewer Paneth cells. Lysozyme-positive cells in the ileal mucosa from patients with IBD decrease remarkably compared with those in control patients. In many cases, lysozyme-positive cells are almost completely undetectable in the ileal mucosal samples obtained from IBD patients, along with massive mucosal erosions and inflammation.[13,41]

HuR deletion causes Paneth cell defects by altering Toll-like receptor 2 (TLR2) activity, since TLR2 serves as an important sensor for autophagy[45,46] and IE-HuR$^{-/-}$ mice do not have the apical distribution of TLR2 in the intestinal mucosa as observed in control mice.[41] TLR2 is localized primarily at the surface of villi and strongly concentrated along the apical area of the small intestinal mucosa in control mice. However, this apical staining of TLR2 in the small intestinal mucosa of IE-HuR$^{-/-}$ mice disappears completely, associated with an increase in the intensity of TLR2 staining in the basal area of the epithelium. The most striking difference between control littermates and IE-HuR$^{-/-}$ mice is the appearance of many areas of small punctate foci of TLR2 in the latter. These punctate regions are located throughout the cytoplasm in the HuR-deficient intestinal epithelium and are regularly identified in every IE-HuR$^{-/-}$ mouse. Similarly, TLR2 distribution in the colonic mucosa is also compromised by HuR deletion, as indicated by a decrease in the apical TLR2 staining in IE-HuR$^{-/-}$ mice. In an *ex vivo* model, TLR2 is normally localized at the luminal regions in primarily cultured intestinal organoids isolated from control mice, but this specific distribution of TLR2 is abolished by HuR deletion, as evidence by the fact that TLR2 staining is diffused in HuR-deficient organoids isolated from IE-HuR$^{-/-}$ mice. On the other hand, HuR deletion fails to alter TLR4 subcellular localization in the intestinal mucosa.

To gain a deeper understanding of the abnormalities of TLR signals in IE-HuR$^{-/-}$ mice, TLR expression was examined and shows that HuR deletion in mice does not alter the levels of total TLR proteins in the intestinal mucosa.[41] Interestingly, HuR deletion decreases the levels of the endoplasmic reticulum (ER) chaperone canopy3 (CNPY3), a protein necessary for the proper subcellular localization of TLR2 on the IEC plasma membrane to carry out secretory autophagy.[47] Reduced levels of CNPY3 by HuR silencing in cultured IECs impair its TLR2 cochaperone function and reduce the apical trafficking for TLR2, leading to an inhibition of TLR2 function. Mechanistically, HuR directly associates with the *Cnpy3* mRNA via coding region (CR) but not its 3′-UTR, and this interaction stabilizes *Cnpy3* mRNA and enhances its translation. HuR knockout reduces CNPY3 levels and thus inhibits the proper folding, subcellular transportation, and apical distribution of TLR2 in the intestinal epithelium. This regulatory role of HuR in TLR2 subcellular distribution through targeting CNPY3 eventually contributes to the control of IEC autophagy activation and innate immunity. In addition, the HuR-deficient epithelium also exhibits decreased levels of IRGM and beclin-1 but increases NLRX1. Since these proteins also modulate TLR activity and autophagy,[45,48] changes in the levels of IRGM, beclin-1, and NLRX1 in IE-HuR$^{-/-}$ mice might be also involved in the mechanisms underlying TLR2 dysfunction and subsequent autophagy inactivation. Recently, HuR is shown to enhance translation of vitamin D receptor that is required for Paneth cell differentiation.[49,50]

Taken together, the findings obtained from human tissue samples, mice with ablated HuR, intestinal organoids, and cultured IECs suggest a novel model by which HuR plays an essential role in the regulation of intestinal epithelial autophagy under pathophysiological conditions (Figure 1). According to this model, HuR enhances intestinal epithelial autophagy by stimulating the expression of ATGs and promoting Paneth cell function, whereas disrupted HuR activity leads to autophagy inactivation and defective Paneth cells, thus compromising the intestinal epithelial defense and promoting the pathological process of mucosal injury and inflammation.

Other RBPs in the regulation of intestinal epithelial autophagy

CUGBP1 binds to a variety of mRNA *cis*-elements, including GREs and AREs, and enhances mRNA decay and/or represses translation of target transcripts in general.[51] CUGBP1 is highly expressed in the intestinal epithelium and its cellular levels and distribution change dramatically in response to

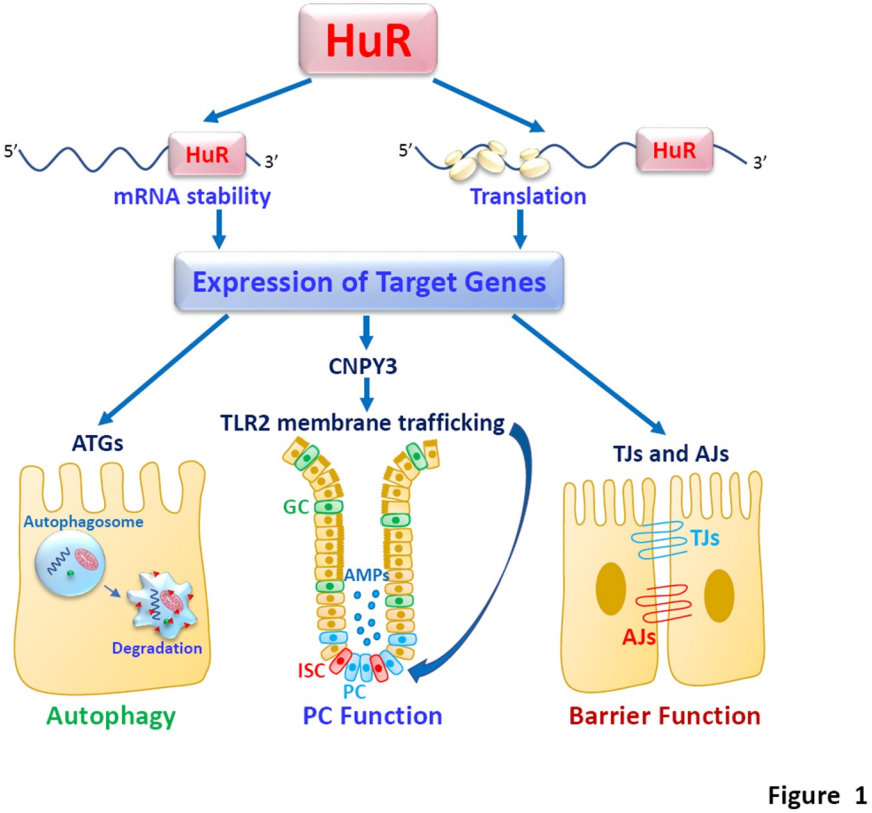

Figure 1

Figure 1. HuR regulates intestinal epithelial defense and barrier by altering stability and translation of its target mRNAs. PC, Paneth cells; GC, Goblet cells; ISC, intestinal stem cells; AMPs, antimicrobial proteins. HuR stimulates epithelial autophagy and barrier function by increasing expression of TJ/AJ and ATGs, but it enhances PC function by manitaining membrane localization of TLR2 via control of CNPY3. HuR activity is tightly regulated by multiple factors, whereas down-regulation of HuR leads to defects in intestinal epithelial autophagy and barrier function.

stressful environments. Several studies have shown that CUGBP1 is a negative regulator of the intestinal epithelium homeostasis and that CUGBP1 and HuR compete for binding to given mRNAs and regulate target transcripts antagonistically.[52,53] Although there is no available evidence showing that CUGBP1 affects the expression of ATGs, CUGBP1 can be involved in the regulation of autophagy indirectly through interaction with HuR.

HuD, ring finger protein 36 (ZFP36)/TTP, and zinc finger protein 423 (ZNF423) also regulate autophagy in other tissues, but their expression levels and functions in the intestinal epithelium remain to be fully investigated. The *Atg5* mRNA is a posttranscriptional target of HuD in pancreatic β cells.[54] Interaction of HuD with *Atg5* mRNA enhances ATG5 translation and thus contributes to the lipidation of LC3 and the formation of LC3-positive autophagosomes. HuD-null mice display lower ATG5 and LC3 levels in pancreatic β cells. ZFP36/TTP promotes *Atg16L1* mRNA decay through directly interaction with AREs located at its 3′-UTR in hepatic stellate cells.[55] Elevation of the ZFP36/TTP levels inhibits macroautophagy activation by decreasing ATG16L1 and plays a crucial role in regulating ferroptosis. Branched-chain amino transferase 1 (BCAT1) is a key regulatory factor of autophagy in pulmonary artery smooth muscle cells and has recently been identified as a potential therapeutic target for the clinical treatment of lung diseases. The function of BCAT1 is remarkably enhanced by the RBP ZNF423.[56] When exposed to hypoxia, ZNF423 is rapidly translocated to the cytoplasm where it binds *Bcat1* mRNA via its 3′-UTR and promotes BCAT1 expression, thus enhancing autophagy activation.

RBPs in regulation of the epithelial barrier function

Intercellular junctions are presented at points of cell-cell and cell-matrix contact in all tissues, particularly in epithelia. The intestinal epithelial barrier depends

on specialized structures of TJ and AJ complexes that are highly dynamic.[2,5] Maintenance of the levels of TJ and AJ proteins is absolutely required for the stability and effectiveness of epithelial barrier structure and function. Several RBPs are intimately implicated in the posttranscriptional control of TJs and AJs in the intestinal epithelial and are crucial for the barrier function.[52,57–59]

HuR enhances expression of TJs and AJs

HuR binds to several mRNAs encoding TJ proteins including claudin-1, claudin-3, occludin and JAM-1, and AJ protein E-cadherin and enhances the stability and translation of these target transcripts.[52,57] Occludin is a transmembrane TJ protein that is necessary for TJ assembly and critical for the maintenance of gut barrier integrity. HuR directly interacts with the 3′-UTR of the *occludin* mRNA and increases occludin translation with a minor effect on its mRNA stability.[52] HuR association with the *occludin* mRNA is regulated through Chk2-dependent HuR phosphorylation. Decreased HuR phosphorylation by Chk2 silencing or by reduction of Chk2 through polyamine depletion reduces HuR-binding to the *occludin* mRNA and inhibits occludin translation, whereas Chk2 overexpression induces HuR/*occludin* mRNA association and promotes occludin expression.

In an *in vitro* permeability model using differentiated IECs, HuR silencing by transfection with HuR-directed small RNA (siHuR) results in the epithelial barrier dysfunction, as indicated by decreased transepithelial electrical resistance (TEER) and increased paracellular permeability.[52,59] Although IE-HuR$^{-/-}$ mice do not exhibit increased gut permeability without any pathological stress, HuR deletion increases the vulnerability of the gut barrier to pathological stress and also inhibits recovery of the barrier functions after treatment with DSS or exposure to cecal ligation and puncture (CLP) and mesenteric I/R.[42,43] In mice exposed to CLP, inhibition of HuR binding affinity for mRNAs encoding TJs and AJs by decreasing Chk2-dependent HuR phosphorylation through polyamine depletion reduces the protein levels of TJs and AJs and slows downs the barrier recovery after septic stress.[14,60] Consistently, PP2A-associated protein α4 stabilizes HuR through a process involving HuR phosphorylation by IκB kinase α, whereas intestinal epithelial-specific ablation of α4 in mice decreases the levels of HuR, leading to an inhibition of TJ expression and gut barrier dysfunction.[61] In addition, HuR also regulates the intestinal barrier function by promoting mucosal renewal, increasing rapid epithelial restitution after acute injury, and protecting IECs against apoptosis. These interesting results have been comprehensively reviewed and nicely summarized in recent publications.[5,16]

CUGBP1 impairs the intestinal barrier function

CUGBP1 negatively regulates intestinal barrier function by repressing the expression of TJs and AJs.[52,59,62] CUGBP1 directly interacts with the mRNAs encoding occludin, claudin-1, and E-cadherin, although it does not bind to the mRNAs encoding claudin-2, claudin-3, claudin-5, ZO-1, and β-catenin. CUGBP1 overexpression specifically inhibits the expression of occludin, claudin-1, and E-cadherin, but fails to alter the levels of other TJs and AJs. This inhibitory effect of CUGBP1 on the expression of given TJs and AJ occurs at the translation level and is mediated through their 3′-UTRs rather than CRs and 5′-UTRs. Ectopically expressed CUGBP1 also damages the epithelial barrier function, as indicated by a decrease in TEER and an increase in paracellular permeability. Interestingly, CUGBP1 and HuR compete for association with the same occludin 3′-UTR and regulate occludin translation competitively.[52,59] Increasing the CUGBP1 levels decreases HuR interaction with *occludin* mRNA and inhibits occludin translation, whereas elevation of HuR levels abolishes CUGBP1 binding to *occludin* mRNA and enhances occludin translation. Studies using purified GST-HuR or GST-CUGBP1 fusion proteins further show that the occludin 3′-UTR interaction with HuR is progressively increased when increasing concentrations of GST-HuR in the binding reaction mixture, but its binding to CUGBP1 is decreased with increasing GST-HuR levels in the mixture. Moreover, cellular levels of CUGBP1 are tightly controlled by protein kinase C (PKC), HuR, miR-503, and polyamines.[60,61,63,64] Activation of PKC increases the stability of CUGBP1 protein through direct phosphorylation.[65] Expression of CUGBP1 in IECs is jointly regulated by HuR and miR-503 at the posttranscription level.[63] HuR associates with the *Cugbp1*

mRNA, increases the loading of polyribosomes onto CUGBP1 transcripts, and thereby increases CUGBP1 translation. In contrast, the interaction of miR-503 with the *Cugbp1* mRNA inhibits its translation by recruiting the *Cugbp1* mRNA to *P*-bodies where mRNAs are sorted for degradation. Cellular polyamines regulate the CUGBP1 expression by altering the level of cytoplasmic HuR and miR-503 abundances.

Other RBPs in the regulation of intestinal barrier function

AUF1 displays a high affinity for ARE-containing RNAs and poly (U) and is involved in many aspects of cellular functions.[66] AUF1 regulates intestinal barrier function via transcription factor JunD that regulates transcription of TJ ZO-1.[67] AUF1 binds to *JunD* mRNA, and this interaction represses JunD expression by destabilizing the *JunD* transcripts in IECs. Association of AUF1 with *JunD* mRNA is tightly regulated by polyamines and HuR (stabilizer of *JunD* mRNA). Polyamines alter *JunD* mRNA degradation by modulating the competitive binding of HuR and AUF1 to the JunD 3′-UTR.[67] Depletion of cellular polyamine increases HuR binding to *JunD* mRNA but decreases the levels of *JunD* transcript bound to AUF1, thus stabilizing *JunD* mRNA. HuR silencing enhances AUF1 interaction with the *JunD* mRNA, reduces the abundance of HuR/*JunD* mRNA complexes, and renders the *JunD* mRNA unstable, thus preventing increases in JunD in polyamine-deficient cells. Decreasing the levels of cellular JunD by AUF1 alters ZO-1 expression and epithelial barrier function.[67]

RBPs TIA-1 and TIAR are highly expressed in the gut mucosa and inhibit the translation of target mRNAs, especially under conditions of stress-associated cellular damage. TIAR binds the 3′-UTR of the mRNAs encoding translation factors and potently suppresses their translation in response to stressful environments.[68] Ectopically expressed TIA-1 and/or TIAR lead to the global inhibition of the cellular translation. Although limited studies are available so far, it has been reported that TIAR directly binds to the *ZO-1* mRNA via its 3′-UTR and this interaction represses ZO-1 translation in IECs, resulting in the epithelial barrier dysfunction.[69] The inhibitory effect of TIAR on ZO-1 translation is enhanced by increasing JunD through stimulation of TIAR/*ZO-1* mRNA association.

LncRNAs in the regulation of autophagy and barrier

LncRNAs are distinct from other well-characterized structural RNAs such as transfer RNAs and ribosomal RNAs and share structural features with mRNAs such as 5′-cap and a 3′-poly (A) tail, but they do not encode recognizable proteins.[19,70] Unlike microRNAs (miRNAs), most lncRNAs are poorly conserved among species and dynamically expressed in tissue-, differentiation stage-, and cell type-specific manners. The levels of cellular lncRNAs are altered rapidly in response to pathophysiological stresses and lncRNAs act as molecular scaffolds, decoys or signals and also function through genomic targeting, *cis*- and *trans*-regulatory factors, and antisense molecules.[71] Generally, nucleus lncRNAs are implicated in gene transcription and chromatin modification, whereas lncRNAs in the cytoplasm regulate the posttranscriptional process through direct interaction with mRNAs, miRNAs, or RBPs. Emerged evidence indicates that lncRNAs regulate the intestinal epithelium homeostasis and are involved in various human diseases.[72–74] Here we highlight the importance of several lncRNAs, including *H19, uc.173*, and *SPRY4-IT1*, in the control of intestinal epithelial autophagy and barrier function and further discuss their implication in the pathogenesis of various gut mucosal disorders.

H19 disrupt the barrier function and suppresses autophagy

Transcribed from the conserved imprinted *H19/igf2* gene cluster, lncRNA *H19* plays a role in diverse cell processes and functions.[75,76] During embryogenesis, the levels of *H19* increase in extra-embryonic tissues, the embryo itself, and most fetal tissues but decrease rapidly after birth.[77] Increased *H19* promotes the expression of imprinted genes and inhibits embryonic placental growth during fetal development.[78] In adult tissues, induction in the levels of *H19* occurs commonly in a broad

spectrum of pathological conditions such as malignancies, inflammation, and after exposure to hypoxia or estrogens.[79–82] Target deletion of *H19* in mice causes an overgrowth phenotype and increases body weight, whereas transgenic re-expression of the *H19* gene prevents the increased growth in mice with ablated *H19*.[77] In the intestinal epithelium, the levels of *H19* increase remarkably in patients with IBD and sepsis and murine gut mucosa with inflammation and erosions, which results partially from an increase in the inflammatory cytokine interleukin-22.[23]

The first evidence demonstrating the importance of *H19* in the regulation of intestinal barrier function is from our observations showing that elevation of the *H19* levels inhibits expression of ZO-1 and E-cadherin.[83] In cultured IECs, ectopically expressed *H19* decreases stability and translation of the *ZO-1* and *E-cadherin* mRNAs, leading to a reduction in the levels of ZO-1 and E-cadherin proteins. Further study reveals that the inhibitory effect of *H19* on ZO-1 and E-cadherin is mediated by miR-675 that is embedded in *H19* exon 1. *H19* does not bind to the *ZO-1* and *E-cadherin* mRNAs but it increases miR-675 production. miR-675 directly interacts with the *ZO-1* and *E-cadherin* mRNAs and inhibits their expression posttranscriptionally. Interestingly, HuR binds to *H19*, inhibits miR-675 processing from *H19*, and decreases the production of miR-675.[83] Ectopic overexpression of HuR rescues the expression of ZO-1 and E-cadherin and prevents the barrier dysfunction in cells overexpressing *H19*. In contrast, intestinal epithelial tissue-specific deletion of HuR in mice enhances miR-675 production and delays the recovery of the gut barrier function after exposure to mesenteric I/R. *H19* also functions as a molecular sponge to decrease the bioavailability of let-7,[79] but decreasing the levels of cellular let-7 fails to alter the expression of ZO-1 and E-cadherin in IECs, suggesting that the association of *H19* with let-7 plays a little role in *H19*-induced inhibition of ZO-1 and E-cadherin and subsequent barrier dysfunction. These results indicate that *H19* and HuR modulate the expression of ZO-1 and E-cadherin and barrier function antagonistically via control of miR-675 processing from *H19*.

A recent study further shows that *H19* actively participates in the regulation of autophagy and functions of Paneth and Goblet cells in the intestinal epithelium.[13] Intestinal mucosal tissue samples from patients with sepsis and septic mice exhibit increased levels of *H19*, associated with autophagy inactivation and defects in Paneth and Goblet cells. Targeted deletion of the *H19* gene in mice increases the function of Paneth and Goblet cells and enhances autophagy in the small intestinal mucosa. The levels of LC3-II, lysozyme, and beclin increase significantly in the H19-deficient epithelium. After exposure to septic stress induced by CLP, *H19* deletion protects Paneth and Goblet cells against septic stress, preserves autophagy activation, and promotes gut barrier function. Compared with intestinal organoids isolated from control littermate mice, organoids generated from $H19^{-/-}$ mice exhibit increased numbers of Paneth and Goblet cells and also display increased tolerance to lipopolysaccharide (LPS). Conversely, ectopic overexpression of *H19* in cultured IECs prevents rapamycin-induced autophagy and abolishes the rapamycin-induced protection of the epithelial barrier against LPS. Although the exact molecular processes by which *H19* regulates autophagy and Paneth and Goblet cells remain largely unknown, available findings indicate that *H19* modulates the intestinal epithelium homeostasis through distinct mechanisms (Figure 2). *H19* disrupts the barrier function by inhibiting ZO-1 and E-cadherin via miR-675 and impairs the epithelium-host defense by inhibiting autophagy and function of Paneth and Goblet cells. Since *H19* also functions as an RNA decoy for miR-34b and let-7 that are also involved in controlling the expression of p53 and other apoptosis-associated proteins,[79,84] it is likely that *H19* can also modulate the epithelium homeostasis by altering the availability of miR-34b and let-7. On the other hand, HuR blocks the processing of miR-675 from *H19* and enhances the epithelial barrier function. Given the fact that intestinal mucosa from patients with critical illnesses exhibits increased *H19* but decreased HuR,[13,41] these exciting findings shed light on developing the new and effective therapeutics to protect the intestinal epithelium integrity through the intervention of *H19* and its regulators such as HuR.

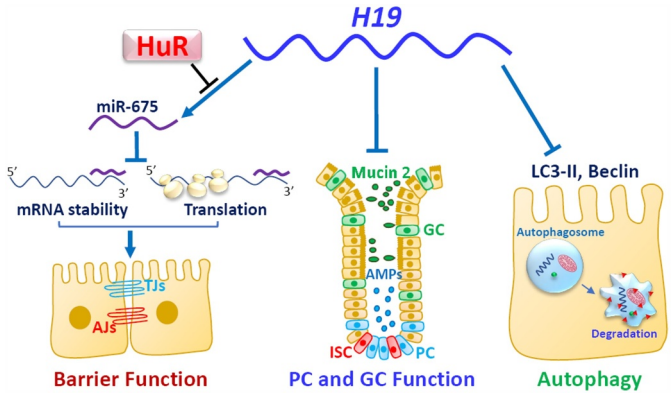

Figure 2. *H19* disrupts the intestinal epithelium homeostasis through several distinct mechanisms. *H19* impairs the epithelial barrier function by inhibiting expression of ZO-1 and E-cadherin posttranscriptionally through release of miR-675 embedded in *H19* exon 1. HuR interacts with *H19*, prevents miR-675 processing from *H19*, and enhances the barrier function. Induced *H19* also inhibits autophagy and lowers Paneth cell (PC) and Goblet cell (GC) function.

Uc.173 enhances the intestinal barrier function

uc.173 is a member of a new class of lncRNAs transcribed from genomic ultraconserved regions (T-UCRs). UCRs are absolutely conserved between orthologous regions of human, rat, and mouse genomes.[73] A total of 481 UCRs have been identified and they are widely distributed among mammalian genomes. Genome-wide T-UCR expression profile analysis reveals 21 T-UCRs, including *uc.173*, differentially expressed in the small intestinal mucosa of fasted mice relative to non-fasted control animals.[73] The expression levels of 18 T-UCRs, including *uc.173, uc.481, uc.356, uc.138A, uc.46A/45A, uc.141, uc.455(8), uc.475, uc.455-(4)*, and *uc.144*, decreased in the intestinal mucosa after a 48-h period of food starvation, while the intestinal mucosal levels of 3 T-UCRs, including *uc.457(E), uc.477*, and *uc.457*(u), increased in fasted mice. Although there are no comprehensive studies investigating the exact roles of all these T-UCRs in the intestinal epithelial homeostasis yet, *uc.173* is shown to be critical for normal gut barrier function.[72]

The expression patterns of *uc.173* in the intestinal epithelium exhibit distinct signature and correlate closely with the status of gut barrier function in response to stressful environments. Intestinal mucosal tissues from patients with IBD display a significant decrease in the levels of *uc.173*, which is associated with a decrease in the levels of TJ expression and epithelial renewal.[72] In cultured IECs, *uc.173* silencing specifically inhibits the expression of TJ claudin-1 and weakens epithelial barrier function. Although systemic administration of locked nucleic acid (LNA) to antagonize *uc.173* (anti-uc.173) has no acute or sub-chronic toxicities in mice, decreasing the levels of tissue *uc.173* by anti-uc.173 increases the vulnerability of the gut barrier to septic stress induced by CLP. Exposure to CLP leads to the gut barrier dysfunction in both anti-uc.173-treated mice and controls, but increased gut permeability following CLP in mice treated with anti-uc.173 is much higher than that observed in control mice. CLP stress also reduces the levels of claudin-1 and claudin-3 in the intestinal mucosa, but inhibition of claudin-1 is amplified by decreasing the levels of *uc.173* in anti-uc.173-treated mice. In support of these findings, *uc.173* also stimulates the renewal of the small intestinal mucosa, since ectopic *uc.173* overexpression increases IEC proliferation and enhances the growth of intestinal organoids.[73]

Further study shows that *uc.173* fails to bind to *claudin-1* mRNA but it enhances translation of claudin-1 through interaction with miR-29b.[72] miR-29b directly associates with *claudin-1* mRNA via its 3′-UTR and inhibits claudin-1 translation. Increasing the levels of *uc.173* decreases the binding of miR-29b to *claudin-1* mRNA and restores claudin-1 expression in cells overexpressing miR-29b. In addition, miR-29b also potently inhibits renewal

of the intestinal mucosa, and elevating miR-29b abundance suppresses mucosal growth and impairs the integrity of the intestinal epithelium.[85] On the other hand, u*c.173* promotes the growth of the small intestinal mucosa primarily by down-regulating miR-195, a repressor of epithelial homeostasis.[73] *uc.173* silencing increases miR-195 expression but does not alter the levels of miR-29b and miR-222.[73] Elevation of the endogenous miR-195 levels by *uc.173* silencing inhibits IEC proliferation, and this effect is almost completely rescued by ectopic transfection of a miR-195 antagomir. Together, the enhancement in intestinal epithelial barrier function by *uc.173* results from antagonizing both miR-29b and miR-195 via distinct mechanisms. Since the basal levels of *uc.173* in the intestinal mucosa are relatively high and changed remarkably in response to stress, *uc.173* plays an essential role in maintaining the intestinal barrier function through interactions with miR-29b and miR-195.

SPRY4-IT1 promotes the epithelial barrier by increasing TJ expression

SPRY4-IT1 (sprouty receptor tyrosine kinase signaling antagonist 4-intronic transcript 1) is a 706-bp lncRNA that is broadly expressed in various tissues. *SPRY4-IT1* is predominantly localized in the cytoplasm and its cellular levels are tightly regulated in response to stress. In the intestinal epithelium, *SPRY4-IT1* induces the TJ expression at the posttranscription level, thus enhancing the gut epithelial barrier function.[57] The levels of *SPRY4-IT1* in the intestinal mucosa from IBD patients decrease significantly, associated with a decrease in the levels of TJs claudin-1, claudin-3, occludin, and JAM-1. In cultured IECs, *SPRY4-IT1* silencing specifically inhibits the expression of these TJs but fails to alter the cellular abundance of ZO-1, E-cadherin, α-catenin, and β-catenin. *SPRY4-IT1* silencing also disrupts the epithelial barrier function in an *in vitro* model, which is overcome by overexpression of claudin-1 or occludin. Elevation of the mucosal levels of *SPRY4-IT1* by infection with a lentiviral-driven *SPRY4-IT* expression vector (lenti-SPRY4-IT1) also protects the gut barrier function in mice exposed to CLP. The decreased levels of TJs by CLP are prevented or significantly reduced by increasing *SPRY4-IT1* in lenti-SPRY4-IT1-infected mice. Mechanistically, *SPRY4-IT1* directly interacts with the mRNAs encoding claudin-1, claudin-3, occludin, and JAM-1, and these interactions stabilize these mRNAs and promote the translation. Moreover, *SPRY4-IT1* also physically associates with HuR and promotes the HuR binding to the TJ mRNAs, thus enhancing HuR-mediated stimulation of TJ expression and gut barrier function.

Other lncRNAs in the intestinal epithelial autophagy and barrier function

Gata6 is involved in regulating the intestinal barrier function by altering epithelial renewal via intestinal stem cells (ISCs).[86] Target deletion of *Gata6* in mice decreases intestinal mucosal growth and disrupts the gut barrier function. *Gata6* directly interacts with two subunits of the NURF remodeling complex and recruits the NURF complex onto the *Ehf* promoter, thus promoting in ISCs the production of EHF, a protein needed for expression of LGR4/5 in ISCs, which in turn stimulates WNT signals. In addition, lncRNAs *BANCR*, *LCPAT1*, and *DRAIC* are also implicated in the regulation of autophagy in other tissues, but their roles in the intestinal epithelium remain unknown. *BANCR* activates autophagy in papillary thyroid carcinoma cells and tissue,[87] and *LCPAT1* is found to accelerate the autophagic flux in lung cancer cells.[88] *LCPAT1* levels increase remarkably in human lung cancer tissues, whereas *LCPAT1* knockdown decreases ATG expression and alleviates autophagy activation induced by rapamycin in lung cancer cells. *DRAIC* is recently identified as a regulator of autophagic flux in MCF-7 breast cancer cells.[89] In an autophagy-independent manner, *DRAIC* silencing inhibits transition from G1 to S-phase during the cell cycle by modulating the activity of ULK1.

Circular RNAs in intestinal autophagy and barrier

Circular RNAs (circRNAs) are a class of widespread and diverse endogenous RNAs that are

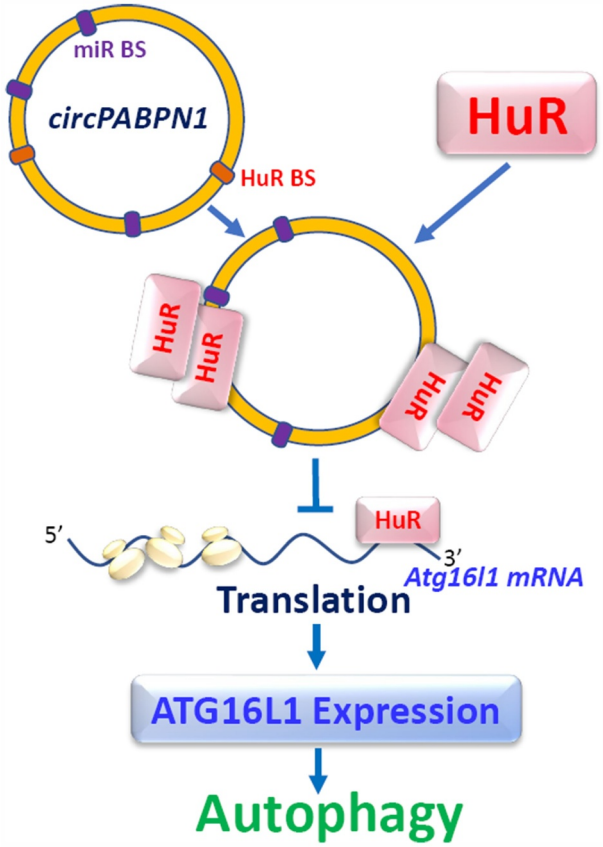

Figure 3. *circPABPN1* regulates ATG16L1 expression through interaction with HuR. miR-BS, microRNA binding site; HuR-BS, HuR binding site. *circPABPN1* does not directly bind to *Atg16l1* mRNA, but it interacts with HuR, forms *circPABPN1*/HuR complex, and reduces availability of HuR for *Atg16l1* mRNA, thus inhibiting ATG16L1 expression.

often expressed in a tissue- and developmental stage-specific manner.[90] Opposite to linear RNAs, circRNAs are covalently closed-loop structures without 5′ to 3′ ends (Figure 3). For many years, circRNAs have only received a little attention, because most classic methods only specifically detect RNA molecules with polyadenylated tails. With the rapid development of new techniques, thousands of circularized transcripts have been identified in various mammalian tissues. Most circRNAs are believed to fulfill noncoding roles,[90] although some circRNAs endogenous to *Drosophila* and human encode proteins.[91] circRNAs harbor single or multiple miRNA-binding sites, and some harbor binding sites for multiple miRNAs.[92,93] Several circRNAs are shown to interact with and 'sponge' miRNAs to decrease the number of freely available miRNAs. For example, *circRS-7* contains multiple sites for miR-7, enabling it to sequester miR-7 and thereby decreasing its availability to target mRNAs bearing miR-7 binding sites.[94] Similarly, *circSRY* functions as a sponge for miR-138, while *circITCH* can interact with miR-7, miR-17, and miR-214.[92,95–97] circRNAs also bind to RBPs to jointly regulate gene expression synergistically or antagonistically.[98,99] It has been reported that HuR associates with many circRNAs and regulates their biological functions in human cervical carcinoma HeLa cells.[100] Differential expression of circRNAs during disease progression suggests the importance of circRNAs in human pathologies.[101]

CircPABPN1 is recently shown to regulate intestinal epithelial autophagy by altering ATG16L1 expression via interaction with HuR.[34] *CircPABPN1* is derived from the *PABPN1* gene and was initially shown to regulate PABPN1 expression by altering HuR binding to *PABPN1* mRNA.[100] Consistent with the findings in HeLa cells, *circPABPN1* interacts with HuR in cultured IECs, and elevation of *circPABPN1* levels specifically abolishes the binding of HuR to *Atg16l1* mRNA and inhibits the expression of ATG16L1 without affecting the expression levels of ATG5 or HuR. Moreover, ectopically expressed HuR partially rescues ATG16L1 expression in cells overexpressing *circPABPN1*, whereas HuR silencing and *circPABPN1* overexpression synergistically inhibit ATG16L1 expression. Since there are no potential binding sites for *circPABPN1* in the *Atg16l1* mRNA, it is likely that *circPABPN1* represses ATG16L1 translation by inhibiting HuR binding to *Atg16l1* transcript (Figure 3). Interestingly, human intestinal mucosal tissues from patients with IBD exhibit increased levels of *circPABPN1* and decreased HuR abundances, along with decreased ATG16L1 and autophagy inactivation. Given the fact that HuR targets multiple transcripts, *circPABPN1* can also regulate different mRNAs through interaction with HuR to alter the intestinal epithelial autophagy and barrier function.

Conclusions and future perspectives

Intestinal epithelial autophagy and intact barrier are essential for maintaining the epithelium homeostasis and health. Disruption of the autophagy and barrier function facilitates the entrance of luminal pathogens into the bloodstream and deteriorates

the progression of many diseases such as IBD, sepsis, Alzheimer's disease, and even aging. Regulation of mRNA stability and translation by RBPs and lncRNAs represents an important layer of complexity governing the gut epithelial defense and barrier function in response to stressful environments. RBPs and lncRNAs have a vast spectrum of biological functions in the intestinal epithelium through interactions with target mRNAs, although the exact roles of most circRNAs in the gut mucosa have not been fully investigated yet. The results summarized here provide evidence that several RBPs and lncRNAs expressed highly in the intestinal epithelium participate in a wide variety of cellular processes and play an important role in intestinal autophagy and barrier function under various pathophysiological conditions. Among RBPs, HuR enhances the epithelium defense by increasing ATG expression and promoting Paneth cell function and it sustains integrity and effectiveness of the barrier function by increasing the expression of TJs and AJs. HuR stabilizes and/or promotes translation of mRNAs encoding ATGs, TJs, AJs, and other barrier-promoting/protecting factors, thus enhancing autophagy and promoting the barrier function. On the other hand, CUGBP1, AUF1, and TIAR destabilize and/or inhibit the translation of these mRNAs, thereby downregulating the autophagy and barrier function. The intestinal autophagy and barrier function are also tightly regulated by two groups of lncRNAs: the negative lncRNA *H19* and positive lncRNAs *uc.173, SPRY4-IT1*, and *Gata6*. HuR interacts with both negative and positive lncRNAs and regulates their binding and biological functions synergistically or antagonistically. Maintenance of autophagy and barrier function is dependent on a dynamic balance between the actions of diverse RBPs and lncRNAs, whereas deregulation of RBPS and lncRNAs contributes to pathologic processes of many human diseases.

Clearly, we have learned and will continue to learn a great deal from studies defining the roles and mechanisms of RBPs and lncRNAs in the intestinal epithelium homeostasis. The critical question is how we can translate these knowledges about RBP/lncRNA-mediated changes into human diseases and potential therapeutic application. We must define the exact mechanisms underlying control of the autophagy and gut barrier function by RBPs and lncRNAs and discover molecular signatures that help to early diagnose the acute gut barrier dysfunction in patients with critical disorders. The exact processes controlling the expression levels of these functional RBPs and lncRNAs in the intestinal epithelium remain largely unknown. A better understanding of the signaling control of epithelial RBPs and lncRNAs, the molecular actions of RBPs and lncRNAs, and the regulation of interactions between RBPs/lncRNAs and their target mRNAs are badly needed. We also need more specific ways to activate or inactivate functions of RBPs and lncRNAs or to stimulate autophagy and gut barrier function. Tissue-specific genetic mouse models will continue to provide important information on the *in vivo* functions of specific RBPs and lncRNAs in the intestinal epithelium. Although studies using human mucosal tissue samples from patients with various critical illnesses are still limited, they are necessary to establish the important impact of altered RBPs and lncRNAs on disease pathogenesis and devise therapeutic venues. With the rapid advance in our understanding of the biology of RBPs and lncRNAs, effective new therapeutics based on targeting RBPs and/or lncRNAs will one day be available to preserve the gut epithelial integrity in the clinical setting.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Abbreviations

RBPs	RNA-binding proteins
ncRNAs	noncoding RNAs
lncRNAs	long ncRNAs
IECs	intestinal epithelial cells
TJs	tight junctions; AJs, adherens junctions
ATGs	autophagy-related genes
IBD	inflammatory bowel diseases
RRM	RNA recognition motif
siRNAs	small interfering RNAs
LC3	light chain 3
TLR2	Toll-like receptor 2
CUGBP1	CUG-binding protein 1
AUF1	AU-binding factor 1
CLP	cecal ligation and puncture
miRNA	microRNA
CNPY3	canopy3
UTRs	untranslated regions
CRs	coding regions
TEER	transepithelial electrical resistance
DSS	dextran sulfate sodium
I/R	ischemia/reperfusion
UCRs	ultraconserved regions
circRNAs	circular RNAs.

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